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Research Article

GASTROINTESTINAL STROMAL TUMORS: CLINICAL, IMMUNOHISTOCHEMICAL, TREATMENT ASPECTS AND PREDICTORS OF SURVIVAL

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ABSTRACT
Gastrointestinal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. This study is a prospective study done from February 2007 to April 2009. The aim of the study was to analyze the clinical, histopathological and immunohistochemical characteristics of patients with GIST, in order to identify variables which influence survival, recurrence and also study the pattern of disease. Over a period of 27 months 34 patients diagnosed with GIST were enrolled into the study. Stomach was the most common site of tumor. Mean age at presentation was 56.08 yrs, GIST's were more common in males with male to female ratio of 2.4:1. There was a significant relationship between tumour size and mitotic activity, and also with increasing Ki proliferative index and other markers such as P53. R0 resection could be achieved in 84% of cases. The use of imatinib as adjunctive therapy in high risk category significantly reduced the recurrence rate as compared to historical control in the literature. Mean actuarial survival was 24.89 months with a mean follow up of 13.5 months.

Keywords: *Gastrointestinal Stromal Tumors, Imatinib, Adjuvant Therapy*

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract, although they account for less than 1% of all GI tumors (Swan and DeMatteo, 2005a). Due to their similar appearance on light microscopy, GISTs were previously thought to be smooth muscle neoplasms, and were classified as leiomyomas or leiomyosarcomas. Mazur and Clark (1983) coined the term GIST, but it was not until the 1990s that this entity was widely recognized. The histological origin of this tumor has been suggested to be the interstitial cell of Cajal (Hirota *et al*, 1998a). This postulate is supported by the finding that GIST has cell markers similar to those of the normal Cajal cell. In 1998 it was discovered that these tumors had *gain-of-function* mutations in the KIT proto-oncogene (Hirota *et al*, 1998b). Approximately 95% of GISTs stain positive for CD117, making it very useful marker for diagnosis (Mietinnem and Lasota, 2001).

GIST may occur along the entire length of GI tract, from esophagus to anus as well as in the omentum, mesentery and retroperitoneum. However they most commonly originate in stomach (60%), followed by the small intestine (30%), the colon and rectum (5%), and the esophagus (5%) (Swan and DeMatteo, 2005b).

This study aims to analyze the clinical and histopathological, and immunohistochemical characteristics of patients with GIST, in order to identify variables which influence survival, recurrence and also study the pattern of disease.

MATERIALS AND METHODS
The study was conducted for a period of 27 months from February 2007 to April 2009 in the department of GI surgery at Lakeshore Hospital and Research Centre, Cochin, Kerala. All the patients who were diagnosed and treated for gastrointestinal stromal tumor were enrolled in the study after taking their consent. Patients were followed up prospectively. Based on clinical presentation, stromal tumors were categorized as primary, recurrent or metastatic.

The surgical philosophy for treatment of GIST is complete surgical removal of gross tumor. Resection was classified as incomplete when gross residual disease was present at the end of resection. Complete resection was considered when all the gross disease was removed regardless of the microscopic margins.
Pathological examination was performed using the following methods:
a) Standard hematoxylin and eosin staining
b) Specific immunohistochemical techniques
c) Tumor was classified into three broad categories: spindle cell, epithelioid type and mixed type.
Based on size and mitotic count tumors were categorized as per Fletcher criteria [5] into different classes.

Table 1: Fletcher criteria [5]

Risk classification	Size (cm)	Mitotic count
Very low risk	< 2	< 5 mitosis/HPF
Low risk	2-5	< 5 mitosis/HPF
Intermediate risk	< 5	6-10 mitosis/HPF
	5-10	< 5 mitosis/HPF
High risk	>10	Any mitosis rate
	> 5	>5 mitosis/HPF
	Any size	>10 mitosis/HPF

Immunohistochemical analysis of tumor sample included markers such as CD 117(C KIT), CD 34, SMA (Smooth muscle actin), and PDGFRα. Expression of KI-67 and p53 was also studied in the histological specimen.
Follow up of the patients was done up to May 2009. All patients underwent 3 monthly checks by clinical examination. Surveillance imaging using ultrasound was performed at 6 monthly intervals and CT scan on a yearly basis or if patients presented with symptoms suspicious of recurrence.
Imatinib mesylate (400 mg/ day) was used as adjuvant therapy in high and intermediate risk group patients (Fletcher criteria). Data analysis was performed using SPSS PC Inc (Version 10) software, Kaplan Meir survival curves were used for survival. Chi square test was used for comparing variables.

RESULTS

From February 2007 to April 2009, 37 patients were diagnosed and for gastrointestinal stromal tumors in the Department of Surgical Gastroenterology, Lakeshore Hospital, Cochin. 3 patients refused to undergo further treatment in our hospital and were excluded from the study. Therefore study of remaining 34 patients revealed following observations.
Age had a unimodal distribution with a mean age at presentation of 56.08 yrs (range 31-83). Majority of patients were in the range of 40-60 yrs.
There were 24 male, 10 female both in similar age range. Male female ratio was 2.4: 1.
Gastrointestinal bleeding and abdominal pain were the most common symptoms at \the time of presentation 12 (35%) patients in each group. In 12 (35%) patients with gastrointestinal bleeding 6 (17.3%) presented with upper GI bleed and another 6 (17.3%) presented with lower GI bleed. Palpable abdominal mass was present in 8 (23.5%) patients. Generalized weakness and weight loss was present in 7 (20.6 %) patients. Other symptoms include constipation in 2, increased frequency of micturition in 2 and urinary retention in 1.
6/34 (17.64%) had been diagnosed incidentally, 5 during laparotomy for other diseases (mainly GI malignancies), and 1 during follow up surveillance in operated case of renal cell carcinoma. Out of the above 6 cases 4 were located in the small bowel and 2 in the stomach.
At time of presentation GIST was localized in nature in 26, locally advanced in 3 and metastatic in 5. All patients underwent blood investigations (Hemogram, renal function test, liver function test). Ultrasound scan of abdomen was performed in 16 patients, CECT scan of the abdomen in 26, Upper GI endoscopy and Colonoscopy were done in 15 and 6 patients respectively depending upon the clinical presentation.

Preoperative biopsy was done in three cases. In first patient who presented with lower GI bleed. Colonoscopy revealed globular submucosal lesion 18 cm above the anal verge and rectal polyp. Biopsy was done to diagnose the nature of lesion Second patient had large locally advanced mass in the pelvis. Percutaneous Tru cut biopsy was done with intention to start neoadjuvant therapy. Third patient had large enhancing mass lesion overlying 2nd and 3rd part of duodenum and head of pancreas suspicious of either neuroendocrine tumor or gastrointestinal stromal tumor. Biopsy was done to confirm the diagnosis of gastrointestinal stromal tumor.

Stomach was the most common site 15/34 (44.1%). Small bowel was the second common site 6/34 (17.65%). In 5 patients tumor was in the duodenum. In 3 patients gastrointestinal stromal tumor was located in the rectum. 2 patients had tumor in the colon. In another 2 patients tumor was in the pelvis, the exact organ of origin could not be determined in both the cases. 1 patient had tumor in root of mesentery.

33/34 patients underwent various surgical procedures (table 5). One patient underwent endoscopic excision biopsy of < 2 cm size nodule located in the antrum of stomach. He had undergone low anterior resection for carcinoma rectum earlier. He presented with melaena in the postoperative period while being on chemotherapy. Urgent upper G I endoscopy revealed bleeding nodular lesion in the antrum of stomach which was managed with snare excision.

Types of surgical procedure done in 34 patients has been summarized in table 2

Table 2: Type of surgical procedure

Organ	Type of procedure	No. of patients (n=34)
Stomach	Laparoscopic assisted wedge resection	2
	Open wedge resection	7
	Wedge resection + splenectomy + metastatectomy	1
	Wedge resection + splenectomy	1
	Subtotal gastrectomy	1
	Endoscopic biopsy	1
	Debulking	1
	Biopsy only	1
Duodenum	Local excision	4
	Whipple's procedure	1
Small bowel	Wedge resection	2
	Segmental resection	4
Colon	Lap assisted sigmoidectomy	1
	Segmental resection	1
Rectum	APER	3
Pelvis	Debulking	1
	Biopsy only	1
Root of mesentery	Debulking	1

**APER – Abdominoperineal excision of rectum*

In summary out of 34 patients 22 underwent local resection, 4- organ resection, 3 required adjacent organ resection in an attempt to achieve R0 resection, 3 patients underewent debulking and in 2 cases only diagnostic biopsy was done.

6/34 (17.6%) patients had post operative complications 1 patient who underwent debulking of a huge pelvic GIST developed renal failure, sepsis and died due to cerebrovascular hemorrhage. 1 patient developed subacute intestinal obstruction following APER for rectal GIST. He was managed conservatively. Intussusception as a complication of feeding jejunostomy catheter developed in 1 patient who had undergone local resection of duodenal GIST. She required reexploration. 2 patients had wound infection. 1 patient had right subclavian vein thrombosis (central line induced) requiring anticoagulant therapy.

Majority of the tumors were more than 10 cm in size 11/34 (32.4%). There were 9 patients (26.5%) each in 5.1-10 cm and 2.1-5.0 cm groups respectively. Only 5 patients (14.5 %) had tumor size less than 2 cm. Mitotic count was < 5 /50 HPF in 14/34(41.2%) cases, 5-10/50 HPF in 14/34 (41.2%) cases and > 10/50 HPF in 6/34 (17.64%) cases.
We observed that size of the tumor correlated directly with number of mitotic figure as shown in table 3.

Table 3: Relationship between size and number of mitosis

Size (cm)	Mean (Mitosis)	No of patients	SD (Standard deviation)
0-2	3.20	5	1.64
2.1-5	4.56	9	2.88
5.1-10	6.78	9	6.38
> 10	15.09	11	25.40
Total	8.35	34	15.22

Pathologically majority of tumors were of spindle cell type 30/34 (88.23%). 3/34 (8.8%) tumors had epithelioid type of cells. Only 1/34 (2.94%) had mixed type of cells.
30/34 (88.24%) tumors were C-KIT positive. 3 patients whose tumors were CKIT negative tumor had positive PDGFRα.
P53 index was > 50% in 13 patients where as 21 patients had > 50% index. Similarly Ki67 > 10% was present in 13 patients. Remaining 21 patients had Ki67 < 10%. On Statistical analysis we observed direct correlation between proliferative index Ki 67 and size of the tumor (Table 4).

Table 4: Comparison of size of tumour and Ki67 proliferative index

Size cm	Ki 67		Total
	<10%	>10%	
<2	4	1	5
2.1-5	8	1	9
5.1-10	5	4	9
>10.1	4	7	11
Total	21	13	34

Chi square test = 6.60, df = 3, p= 0.084

Tumor necrosis was present in 22/34(64.7%) tumors, whereas 19/34(55.8%) tumors had intratumoral hemorrhage.

Risk Classification

Using Fletcher criteria of size and number of mitosis / 50 HPF, tumors were categorized. 18/34(52.94%) were of the high risk category. 6/34 (17.64%) were of intermediate risk. There were 10 patients in low and very low risk group (29.41%).
Imatinib mesylate (Glivec, Novartis Pharma AG) was given to high risk and intermediate risk group patients as adjuvant therapy. Very low and low risk patients were on follow up surveillance only. Imatinib was prescribed as 400 mg/ day dosage. 24 patients out of 34 were of high and intermediate risk category. 20/24 patients received imatinib. 16 patients received imatinib after complete resection (adjuvant), 2 patients with unresectable metastatic disease (therapeutic), 1 patient as neoadjuvant and 1 after debulking.
Imatinib mesylate was tolerated well by majority of our patients. Adverse reaction was noted in 4/20 (20%) patients. These adverse reactions were: Facial edema (1), Facial hypopigmentation (1), Cellulitis with pedal edema (2), Fever with pruritis (1). Two patients required temporary cessation of imatinib due to cellulitis and edema in the legs. Imatinib was restarted at interval of two weeks with reduced dosage of 200 mg/ day. None of the patients had any alteration in complete blood count or liver function test.
All patients with the diagnosis of GIST were followed up regularly in the outpatient department of surgical gastroenterology. Patients with high and intermediate risk of recurrence were followed up at the

interval of 3-4 months. Patients with very low and low risk were followed up every 6 months. Adjuvant chemotherapy with Imatinib mesylate (400 mg/day) for high and intermediate risk was given in cooperation with medical oncology department. Irrespective of symptoms ultrasound was done every 3-4 months and CT scan was done at the end of every 12 months. Record of any adverse effect due to imatinib was also noted.

Mean follow up was for 13.5 months (Range 1-27 months, SD=8.11).

There were 3 deaths. In one patient death was secondary to cerebrovascular hemorrhage after debulking surgery of pelvic GIST. 2 other patients died due to unrelated cause. One died because of adverse reaction to chemotherapy given for carcinoma rectum. Second patient in whom GIST was diagnosed incidentally in the proximal jejunum while undergoing laparotomy for carcinoma stomach died due to recurrent carcinoma stomach. Using Kaplan Meir survival curve, mean survival time was 24.89 months (SE-1.15, 95% confidence interval [22.63, 27.16]).

Survival analysis for follow up

Time	Status	Cumulative Survival	Standard Error	Cumulative Events	Number Remaining
1.00	0, 00			0	33
1.00	0, 00			0	32
1.00	0, 00			0	31
1.00	0, 00			0	30
3.00	1, 00	0, 967	0, 0328	1	29
4.00	0, 00			1	28
5.00	0, 00			1	27
6.00	0, 00			1	26
6.00	0, 00			1	25
8.00	0, 00			1	24
11.00	1, 00	0, 924	0, 0504	2	23
11.00	0, 00			2	22
11.00	0, 00			2	21
12.00	1, 00	0, 883	00645	3	20
12.00	0, 00			3	19
12.00	0, 00			3	18
12.00	0, 00			3	17
12.00	0, 00			3	16
13.00	0, 00			3	15
16.00	0, 00			3	14
17.00	0, 00			3	13
17.00	0, 00			3	12
19.00	0, 00			3	11
20.00	0, 00			3	10
20.00	0, 00			3	9
21.00	0, 00			3	8
21.00	0, 00			3	7
22.00	0, 00			3	6
22.00	0, 00			3	5
22.00	0, 00			3	4
25.00	0, 00			3	3
26.00	0, 00			3	2
27.00	0, 00			3	1
27.00	0, 00			3	0

2 patients who had metastatic disease at the time of presentation also received imatinib. In one patient there was no progression of disease at 21 months of follow up. In another patient follow up CT scan showed reduction in size of the lesion (follow up at 22 months post therapy).

DISCUSSION

Gastrointestinal stromal tumor is an uncommon visceral tumor that arises predominantly in the gastrointestinal tract.

In this study we analyzed the clinicopathological features of gastrointestinal stromal tumors treated in surgical gastroenterology department of Lakeshore Hospital, Cochin. The outcome after surgical therapy and the role of molecular targeted of therapy in management was also studied.

The mean age of patients was 56 years, which was consistent with what is reported in the western literature (Dematteo, *et al*, 2000) However two studies in the Indian subcontinent had shown the median age to be 50 years, a decade lower than what is reported in the literature (Rajappa *et al.,* 2007a; Rauf *et al.*, 2007a).

In our group of patients there were more male patients as compared to female as evident by the male female ratio of 2.4:1. Most other series have reported only a slight male preponderance. Consistent with our results Rajappa *et al.,* (2007 b) and Rauf *et al.,* (2007 b) had shown male female ratio of 2:1.

In our study group predominant presenting symptoms were gastrointestinal bleeding and abdominal pain 24/34(70.5%). In a retrospective study by Rabin *et al.,* (2009) gastrointestinal bleeding was reported as the commonest presenting symptom. Whereas various other studies had shown abdominal pain Rajapa *et al.,* (2007 c); Claudia *et al.,* (2007 a), gastrointestinal bleeding (Dematteo *et al.,* 2000 b) or gastrointestinal bleeding, abdominal pain and mass as the commonest presenting symptoms (Hueman, 2008)

6/34 (17.64%) patients were diagnosed incidentally. 6/34patients were associated with co existent epithelial cell malignancy. Colorectal carcinoma was found to be the most commonly associated malignancy in our patients. Majority of the incidentally detected GISTs were small tumors and were equally distributed in the small bowel and stomach. The incidence of incidental diagnosis 17.64% in our series is higher than what is reported in the literature i.e 5% by DeMatteo *et al.,* (2000 c) and 14% by Wronski *et al* (2006).

The assessment of actual incidence of incidental GIST associated with epithelial cell malignancy is difficult, because most of the data is based on patients undergoing surgical treatment, whereas epithelial cell malignancy patients managed with non-surgical measures are unaccounted. Moreover, intraoperative identification of GIST is incidental rather than intentional as a result many lesions may be missed.

At presentation 26/34 (76.4%) had localized tumors where as 5/34(14.7%) were metastatic. Only 3/34(8.8%) patients had locally advanced tumors. DeMatteo *et al.,* (2000 d) in their series of 200 patients had shown that 46% of patients had localized disease and 47% of patients presented with metastatic disease. Roberts *et al.,* (2002) in a study on clinical presentation of gastrointestinal stromal tumors quoted that between 15 -50% of GIST's presented with overtly metastatic disease. Perez *et al.,* (2006) after analysis of SEER database from 1992-2002 showed that 51% of GIST were localized, 19% had regional spread and 23% had distant metastases. Similarly Claudia *et al.,* (2007 b) in a population based study showed that 21% patients had metastatic disease at presentation.

Using the risk of aggressive behavior classification proposed by Fletcher tumors were classified as very low risk 5/34 (14.7%), low risk 5/34(14.7%), intermediate risk 6/34(17.6%) and high risk 18/34(52.9%) groups. Our results are consistent with the reported incidence in literature (Rajappa *et al.,* 2007; Claudia *et al.,* 2007; Judson *et al.,* 2006; Unalp *et al.,* 2009; Alberto *et al.,* 2008).

In our study out of the 24 patients in the high and intermediate risk category, Imatinib mesylate (400mg/day) was used in 20 patients. In 16 patients it was prescribed as adjuvant therapy after R0 resection. These patients were followed up for a mean period of 13.5 months (range 1-27 months). Ultrasound scan of the abdomen was done every 3-4 months interval and CT scan of the abdomen was performed every one year. None of these patients showed any evidence of recurrence. This is in contrast to historical data where it has been shown that recurrence occurs in 40-50% patients after complete

surgical resection alone in high and intermediate risk group patients. This could be attributed to policy of R0 resection careful handling of tumor to avoid rupture and use of imatinib as adjuvant therapy. Our result was consistent with the reported results on the use of adjuvant therapy in the literature. The American college of surgical oncology group (ACOSOG) study Z 9000, a phase II study showed 1, 2 and 3 year recurrence free survival of 94, 73 and 61% respectively (Dematteo *et al.,* 2005). Similarly Nilsson *et al*, (2007) in a study on 23 GISTs patients receiving adjuvant imatinib showed a statistically significant improvement in outcome after a mean follow up of 3 years. Only 1 of 23 patients in the adjuvant group relapsed compared with 32 of the 48 patients without treatment (p=0.001). The results of ACOSOG Z 9001 trial demonstrated improved recurrence free survival for patients receiving adjuvant imatinib, however there was no improvement in overall survival when compared with the placebo group (Dematteo *et al.,* 2009).

In our series 2 patients with unresectable metastatic disease on palliative imatinib therapy showed stable disease on follow up CT scan. One patient in whom imatinib was started after debulking surgery showed reduction in size of tumor on follow up CT scan after 1 year.

Although there are case reports on successful use of imatinib as neoadjuvant therapy in locally advanced disease resulting in organ preserving surgery (Lo *et al.,* 2005; Shah *et al.,* 2005; Salazar *et al.,* 2006; Hou *et al.,* 2009). Our experience in one case of locally advanced pelvic GIST was disappointing. Despite 6 weeks of therapy there was no reduction in size on follow up CT scan.

Conclusion

In our prospective study of 34 patients with diagnosis of GIST over a period of 27 months, majority of tumor aroused from the stomach. R0 resection could be achieved in 84% of cases. Mean actuarial survival was 24.89 months with a mean follow up of 13.5 months. There was a significant relationship between tumour size and mitotic activity, and also with increasing Ki proliferative index and other markers such as P53. Recurrence after complete tumor excision did not occur in any patient. The use of imatinib as adjunctive therapy in high risk category significantly reduced the recurrence rate as compared to historical control in the literature. Although numbers are small and follow up is short, it may well be due to use of postoperative adjuvant imatinib.

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